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TITLE: A Population-Based Randomized Trial to Assess the Effects of Short-Term Cessation of Hormone Replacement Therapy on Mammography Assessments and Breast Density

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14. ABSTRACT This randomized controlled trial is designed to test whether short-term (1-2 months) hormone replacement therapy (HRT) cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of HRT cessation. The study is being conducted at Group Health, a managed health care organization with an organized breast cancer screening program. We project recruiting about 1,500 women who will be randomized to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We are measuring breast density using a computer-assisted method and mammography recall rates from an expert radiologist review of the mammograms; both readers will be blinded to HRT status. Recruitment started 11/2004; through 5/16/2007, we have contacted 5,435 potentially eligible women. Among those, 36% have agreed, 38% have refused and 25% have been ineligible. Among women who have agreed to participate, 29% have withdrawn from the study. We will continue to recruit women through August 2007.					
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INTRODUCTION:

This randomized controlled trial is designed to test whether short-term (1-2 months) hormone replacement therapy (HRT) cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend by duration of HRT cessation. The study is being conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. We are using automated data to identify HRT users who are due for screening mammograms. Women are being recruited through mailed correspondence and telephone contact. We are projecting to recruit about 1,500 women to randomize to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We are measuring breast density using a computer-assisted method. Mammography recall rates are being determined from an expert radiologist review of the mammograms. Both readers are blinded to HRT status. We will test whether: 1) HRT cessation 1 or 2 months before a screening mammogram reduces the likelihood of receiving a recommendation for additional evaluation (recall) compared to women who continue using HRT; 2) HRT cessation for 1 versus 2 months affects the likelihood of receiving a recommendation for additional evaluation; and 3) there is a greater change in breast density (to lower breast density) among women who stop HRT 1 or 2 months before a screening mammogram to those who do not stop HRT. Change in breast density will be measured as the difference between breast density on the screening mammogram before the trial (while on HRT) and on the mammogram during the trial. As part of this trial we will also evaluate: 1) women's tolerance (defined as continued cessation) for short-term (1-2 months) HRT cessation, 2) the rate of HRT re-initiation after participation in the trial, and 3) rates of reported adverse events (return of hot flashes, thromboembolic events within the first 6-months after re-initiation, and return of bleeding with re-initiation among previously amenorrheic women) across randomization groups.

BODY:

Progress on the scope of work (SOW) outlined in the original proposal.

Task A. Recruit 1500 women to participate in the trial

Study recruitment began in November 2004, after final HSRRB approval. In the ensuing 31 months we have contacted 5,435 women, an average of 175 per month.

Current Recruitment (5/16/2006):

Selected	5435		
Contacted	5209	95.8%	% of selected
Ineligible	1321	25.4%	% of contacted
Eligible	3888	74.6%	% of contacted
Refused	1999	51.4%	% of eligible
Agreed	1889	48.6%	% of eligible
Withdrew before consent	369	19.5%	% of agreed
Withdrew after consent	173	9.2%	% of agreed
Total withdrew after recruited	542	28.7%	% of agreed
Study participants	1347	25.9%	% of contacted

In our original proposal, we estimated an enrollment of 21.9% of the women approached. We are above target by recruiting 25.9% of women approached. However, the pool of potentially eligible women declined in the wake of the report of adverse effects of hormone therapy from the Women's Health Initiative in July 2002. HRT use has decreased among members of GHC to less than 30% of the levels in 2001 and the number of potentially eligible women has slowly dropped each month. We are approaching all potentially eligible women.

With the supplemental funds awarded in 2006, we have extended recruiting for 15 months beyond the original end date for recruiting of 5/31/2006 to 8/31/07 and expect to meet the recruiting goal.

Task B. Develop Study Materials

The study staff developed study materials and received approval for all materials from the GHC HSRC and the HSRRB. Study staff met with the Advisory board members once during the last year to go over recruitment and participant materials.

Task C. Monitor the safety of HRT cessation and initiation

The Study Nurse has collected information on all adverse events identified from self-report, toll free phone number, or automated administrative data. The study team has followed all procedures for reporting Adverse Events to GHC HSRC and DOD HSRRB. The programmer has reviewed automated administrative data each month to extract information on women enrolled in the study to identify adverse events noted in in-patient and out-patient procedures using ICD-9 and CPT codes. The study physician and study monitor have reviewed all adverse events identified from self-report, toll free phone number, or automated administrative data for relationship to study participation. The study biostatistician has generated and distributed one Data Safety and Monitoring Board report to the DSMB. The Data Safety Monitoring Board met once during this period (May 29, 2007) to review study progress and safety.

Task D. Ascertain outcomes from mammograms (mammographic density and clinical interpretation)

The first reviews of mammograms for density and clinical assessment were completed in June 2005. Since then the study radiologist has assessed 1045 mammograms of the 1112 clinical mammograms on study participants available (94%) and the Research Specialist has entered information from the radiology assessment form into the mammogram database. The Research Specialist has also digitally scanned each study subject's baseline and follow-up mammograms for density determination. Monitoring GHC automated pharmacy data for reinitiation of HRT is ongoing. 1104 women have returned a follow-up questionnaire that includes questions on their intention for restarting HRT and compliance with HRT cessation during the study. The questionnaire is mailed to women two weeks before their mammogram appointment.

Task E. Data quality and control

Questionnaires are scanned weekly using Teleform technology that has built-in logic checks for the data. The radiologist fills out the Radiology Assessment form for each subject after completing reading the mammograms and the Research Specialist enters the form data into the mammogram database. The study programmer runs quality checks on those data monthly. The quality control digital images are being randomly selected, rescanned and re-read for density outcomes on an ongoing basis.

Task F. Final analyses and report writing

Task F is not complete; both elements require data collection to be completed. Preliminary data about the study were presented in June 2005 at the DoD's Era of Hope meeting (see reference section below).

KEY RESEARCH ACCOMPLISHMENTS:

REPORTABLE OUTCOMES:

Recruitment of study subjects began in November 2004. To date, we have no reportable outcomes.

CONCLUSIONS:

We are experiencing a higher proportion of refusals and withdrawal after agreeing to participate in the trial than expected based on other GHC recruitment studies and our pilot data collected before grant submission. In 2004, we spent considerable time talking with our survey department and lay advisory committee to determine ways we could improve the recruitment materials to address the concerns and/or questions of women who are refusing and again in 2006 conducted another review of materials and procedures. We made modifications to our recruitment materials that addressed issues brought up by the survey department: 1) how participation will directly influence women, and 2) the case of women who cannot comply with staying off hormones if they are

randomized to one of the 2 cessation arms that were reviewed and approved by our local IRB (June 2005) and the HSRRB (September 2005).

One of our key findings to date is that the cohort of women who are still using HRT following the results of the Women's Health Initiative (WHI) may be substantially different than women who were using before WHI. As such, understanding whether this intervention would be acceptable to women still using HRT is likely to be a more important focus of this study than previously expected at grant submission. For example, if we find that women who stop using hormones have a significant reduction in breast density and/or recall rates, it may be that the intervention is still unacceptable to the majority of women who are still using HRT. We are collecting information on compliance, reinitiation and symptoms, so we will be well positioned to address acceptability of the intervention.

REFERENCES:

Buist DSM, Newton KM, Reed S, Anderson ML, Aiello EA, King E, Palmer L, Seger, D. Can Short-Term Hormone Therapy Cessation Before Mammography Decrease Breast Density And Improve Mammography Performance? A Randomized Trial. Department of Defense's Era of Hope. June 8-11, 2005. Philadelphia, PA.